MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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Office of Counter-Terrorism and Pediatric Development

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review: Drug Use Data
Sodium Ferric Gluconate Complex (Ferrlecit®, NDA 20-955)
Pediatric Exclusivity Grant Date: March 24, 2004

****This document contains proprietary data from IMS Health and Premier which cannot be shared outside of FDA without clearance from IMS Health and Premier obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines the drug use for Ferrlecit® (sodium ferric gluconate complex in sucrose injection) in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on March 24, 2004. Proprietary drug use databases licensed by the Agency were used to conduct this analysis. The IMS Health, National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution. It was clear from these data that this product was mainly sold into non-retail settings; 99.3% of all vials sold were to non-retail pharmacies during the 12-month period from April 2004 through March 2005. Of these vials sold to non-retail pharmacies, 70.3% were sold to clinics. Since the Agency does not have access to data describing the use of

drug products in clinics, we could only examine the utilization patterns for Ferrlecit® focusing on the inpatient setting. Inpatient use was assessed from hospital billing data provided by Premier™. *It should be noted, however, that the inpatient use described in this report likely reflects only a quarter of the total sales of Ferrlecit®.*

Overall, the inpatient use of sodium ferric gluconate (Ferrlecit®) appears to be increasing over the two year study period from 11,521 discharges during year 2003 to 13,899 discharges during year 2004. However, use in the pediatric population is uncommon. Use of sodium ferric gluconate was almost exclusively in the adult population discharged from Premier's acute care hospitals. Over the two-year time period surveyed, pediatric use (patient ages 0-16) remained steady at less than 1% of all discharges billed for sodium ferric gluconate.

In the subset of 37 pediatric hospitals, the use of sodium ferric gluconate in the pediatric population (ages 0-16) was also low. A total of 16 discharges were captured during the year 2003 and 24 discharges were captured during year 2004, representing approximately 9% - 12% of billing for all injectable iron products, including iron dextran and iron sucrose. Of the three injectable iron products, iron dextran was billed most frequently with approximately 150 discharges (77.3%), followed by iron sucrose with approximately 20 discharges (10.3%) in year 2004.

A major limitation of the current analysis is that the data resources available to the Agency do not capture use of Ferrlecit® or other injectable iron products in the outpatient clinic setting.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of that act requires the reporting of adverse events associated with the use of a drug in children during the one year following the date on which the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Ferrlecit® (NDA 20-955, sodium ferric gluconate complex in sucrose injection) was approved on February 18, 1999, for the treatment of iron deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Ferrlecit® (NDA 20-955) on March 24, 2004. On August 13, 2004, the product was approved under supplement SE5-006 for the treatment of iron deficiency anemia in pediatric patients 6 years and older undergoing chronic hemodialysis who are receiving supplemental epoetin therapy.

Ferrlecit® is supplied in colorless glass ampules containing 62.5 mg of elemental iron in 5 mL for intravenous use and packaged in cartons of 10 ampules.

This review describes only inpatient drug use patterns for Ferrlecit® (NDA 20-955, sodium ferric gluconate complex in sucrose injection) in the pediatric population as well as in the adult population in the years prior to and subsequent to the granting of pediatric exclusivity. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

METHODS

A. Determining Setting of Use

IMS Health, National Sales Perspectives™ data were used to determine the setting in which the product was sold. Sales of this product by number of vials or eaches sold from the manufacturer to various retail and non-retail channels of distribution were analyzed[1]. It was clear from these data that this product was mainly sold into non-retail settings; 99.3% of all vials sold were to non-retail pharmacies during the 12-month period from April 2004 through March 2005. Of these vials sold to non-retail pharmacies, 70.3% were sold to clinics. Since the Agency does not have access to data describing the use of drug products in clinics, we could only examine the utilization patterns for Ferrlecit® focusing on the inpatient setting. Therefore, a major limitation of the current analysis is that the data resources available to the Agency do not capture use in the outpatient clinic setting. Inpatient use was assessed from hospital billing data provided by Premier™. *It should be noted, however, that the inpatient use described in this report likely reflects only a quarter of the total sales of Ferrlecit®.*

We examined the sales and inpatient drug use patterns for Ferrlecit® and two other injectable iron products, iron sucrose (Venofer®) and iron dextran (Infed®) to compare Ferrlecit® use, to other products of the same therapeutic class.

B. Data Resources

IMS HEALTH, NATIONAL SALES PERSPECTIVES™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

For this analysis, the sales trend for Ferrlecit® (NDA 20-955, sodium ferric gluconate complex in sucrose injection) was examined from April 2002 to March 2005, inclusive.

[1] IMS Health, IMS National Sales Perspectives™, Year 2004, Extracted May 2005. Original File: 0505fer1.dvr.

PREMIER™

Premier maintains a large hospital drug utilization and financial database which contains billing information from over 450 acute care facilities and includes approximately 14 million inpatient records. Roughly one out of every seven inpatient discharges in the United States is represented in Premier's database.[2] Data are available from January 2000 through the present, but have a lag time of approximately 6 months.

The hospitals that contribute information to this database are a select sample of both Premier and U.S. institutions, and do not necessarily represent all hospitals in the U.S. Data are collected from this sample of participating hospitals with diverse characteristics based upon geographic location, number of beds, population served, payors, and teaching status. The data collected include demographic and pharmacy-billing information, as well as all diagnoses and procedures for every patient discharge. Preliminary comparisons between participating Premier hospital and the probability sample of hospitals selected for the National Hospital Discharge Survey (NHDS) appeared to be very similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups.[3] However, it is unknown whether drug use in the Premier hospitals can be projected to all hospitals in the U.S. Moreover, national estimates for the pediatric inpatient population based on the Premier database may not be reliable, as children admitted to general hospitals are likely to be different from those admitted to children's hospitals with regard to drugs administered in hospital, and thus, would be weighted differently in a projection model. Therefore, only actual discharges were examined.

For this analysis, the total number of actual discharges associated with Ferrlecit® (NDA 20-955, sodium ferric gluconate complex in sucrose injection), including iron sucrose (Venofer®) and iron dextran (Infed®) within Premier hospitals was examined for the time period from January 2003 to December, 2004, inclusive.

PREMIER PEDIATRIC™

Premier's pediatric database is a subset of the larger database described above. Information is available from 37 pediatric hospitals. Data are also available from January 2000 through the present, but have a lag time of approximately six months.

For this analysis, the total number of actual discharges associated with Ferrlecit® (NDA 20-955, sodium ferric gluconate complex in sucrose injection), including iron sucrose (Venofer®) and iron dextran (Infed®) use within this subset of 37 children's hospitals is examined from January 2003 to December, 2004, inclusive.

[2] National center for Health Statistics. Health, United States, 2003

[3] Staffa JA, Gutierrez B, Kornegay C, et al. Outcome-based evaluation of a method for obtaining U.S. national estimates of inpatient drug utilization. Pharmacoepidemiol Drug Saf 2003;12: S173

RESULTS

I. Inpatient Use and Demographics

Acute Care Hospitals

Overall, the inpatient use of sodium ferric gluconate (Ferrlecit®) appears to be increasing over the two year study period from 11,521 discharges during year 2003 to 13,899 discharges during year 2004 (Table 1). Use of sodium ferric gluconate is primarily in the adult population. Over the two-year time period surveyed, pediatric use (patient ages 0-16) remained steady at less than 1% of all discharges billed for sodium ferric gluconate. In adults (ages 17 and older), "hemodialysis" (ICD-9 39.95) was the most frequent procedural diagnosis associated with discharges in which sodium ferric gluconate was billed[4]. This diagnosis was present in approximately 10.3% or 1434 of adult discharges during year 2004. In the pediatric population, procedures and diagnoses varied greatly and there was only one discharge in which a procedural diagnosis of "hemodialysis" occurred.

Table 1: Total Number of Actual Discharges in which Sodium Ferric Gluconate, Iron Dextran or Iron Sucrose Were Billed by Age Groups in Premier Hospitals, January 2003 through December 2004 (Rx Market Advisor™)

	2003		2004	
	Discharges	%	Discharges	%
Sodium ferric gluconate	**11,521**	***100.0***	**13,899**	***100.0***
Patient Age 0-16	**33**	***0.3***	**37**	***0.3***
Patient Age 17 and Older	**11,488**	***99.7***	**13,862**	***99.7***
Iron Dextran	**7,259**	***100.0***	**6,327**	***100.0***
Patient Age 0-16	**352**	***4.8***	**315**	***5.0***
Patient Age 17 and Older	**6,907**	***95.2***	**6,012**	***95.0***
Iron Sucrose	**5,584**	***100.0***	**10,630**	***100.0***
Patient Age 0-16	**521**	***9.3***	**2,370**	***22.3***
Patient Age 17 and Older	**5,063**	***90.7***	**8,260**	***77.7***

Discharges do not add up to 100% due to discharges with missing age information
Premier Rx Market Advisor, data extracted June 2005.

[4] Premier 6-20-05 Sodium ferric iron sucrose iron dextran.xls

Pediatric Care Centers

In the subset of 37 pediatric hospitals, the use of sodium ferric gluconate in the pediatric population (ages 0-16) was low. A total of 16 discharges was captured during the year 2003 and 24 discharges were captured during year 2004, representing approximately 9% - 12% of billing for all injectable iron products, including iron dextran and iron sucrose (Table 2). Of the three injectable iron products, iron dextran was billed most frequently with approximately 150 discharges (77.3%), followed by iron sucrose with approximately 20 discharges (10.3%) in year 2004.

Table 2: Total Number of Actual Discharges in which Sodium Ferric Gluconate, Iron Dextran or Iron Sucrose Were Billed in Premier Pediatric Hospitals (Age 0-16 years), January 2003 through December 2004 (Rx Market Advisor™)

Drug Name	2003		2004	
	Discharges	%	Discharges	%
Total	**180**	**100.0%**	**194**	**100.0%**
Iron Dextran	**152**	**84.4**	**150**	**77.3**
Iron Sucrose	**12**	**6.7**	**20**	**10.3**
Sodium Ferric Gluconate Complex	**16**	**8.9**	**24**	**12.4**

Premier Pediatric Rx Market Advisor, data extracted June 2005.

DISCUSSION

Based on data reflecting inpatient use, the use of Ferrlecit® is uncommon in the pediatric population. Overall, the inpatient use of Ferrlecit® is primarily in the adult population and appears to be increasing over the two year study period. The observed increase in discharges, in which Ferrlecit® was billed, does not appear to be the result of increasing number of hospitals in the sample. The average number of reporting hospitals in Premier sample for 2003 was 403; for 2004, it decreased to 356 hospitals.

Until the recent approval of Ferrlecit® for pediatric use in 2004, the primary agent used for iron replacement therapy was iron dextran. However, iron dextran is associated with significant adverse effects such as anaphylaxis and death. Michael et al. found that the incidence of adverse effects was significantly less with Ferrlecit (0.44%; confidence interval (CI) 0.21-0.71%) compared to iron dextran (2.47%; CI, 1.87-3.07%; $P < 0.0001$) and no difference in serious adverse effects was found between placebo and Ferrlecit®.[5] These results may ultimately influence drug utilization of Ferrlecit® in inpatient and outpatient settings. While these findings of improved drug tolerance in adults may suggest that shifting preference towards sodium ferric

[5] Michael B, Coyne DW, Fishbane S, et al; Ferrlecit Publication Committee; Sodium ferric gluconate complex in hemodialysis patients: adverse reactions compared to placebo and iron dextran**.** Kidney Int 2002; 61(5):1830-9

gluconate over dextran is likely, no evidence of such a shift has yet been seen in the pediatric population.

Findings from this consult should be interpreted in the context of the known limitations of the databases used. The IMS Health, National Sales Perspectives™ does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients receiving these products, such as age and gender. The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Premier data are derived from an administrative secondary database that is primarily collected for billing purposes. Changes in policy or payment procedures may influence the data collected because of their administrative nature. Therefore, drug use information from such a database can only be used as an estimate for evidence of use during hospitalization.

Finally, our analysis was conducted using inpatient database. Currently, the data resources available to the Agency do not capture use of Ferrlecit® or other injectable iron products in the outpatient clinic setting. Yet, use of Ferrlecit® in the pediatric population undergoing chronic hemodialysis therapy is expected to occurred mainly in the outpatient clinic setting, where most of the kidney dialysis treatment in the U.S. is currently provided. According to the United States Renal Data System (USRDS), the number of dialysis clinic centers nationally was 4,204 at the end of year 2002.[6] Moreover, sales data suggest that inpatient use represents only a quarter of total product use. Therefore, the lack of data on outpatient clinic setting is a major limitation of the current analysis.

CONCLUSION

Overall, the inpatient use of sodium ferric gluconate (Ferrlecit®) in the inpatient setting appears to be increasing over the two year study period from 11,521 discharges during year 2003 to 13,899 discharges during year 2004. However, use in the inpatient pediatric population is uncommon; use of sodium ferric gluconate was almost exclusively in the adult population discharged from Premier's acute care hospitals. Over the two-year time period surveyed, pediatric use (patient ages 0-16) remained steady at less than 1% of all discharges billed for sodium ferric gluconate.

In the subset of 37 pediatric hospitals, the use of sodium ferric gluconate in the pediatric population (ages 0-16) was low. A total of 16 discharges were captured during the year 2003 and 24 discharges were captured during year 2004, representing approximately 9% - 12% of billing for all injectable iron products, including iron dextran and iron sucrose. Of the three injectable iron products, iron dextran was billed most frequently with approximately 150

[6] U.S. Renal Data System. 2004 Annual Data Report: Atlas of End-Stage Renal Disease in the United States [on-line]. Available from URL: http://www.usrds.org/ (Accessed 2005 March 16).

discharges (77.3%), followed by iron sucrose with approximately 20 discharges (10.3%) in year 2004.

A major limitation of the current analysis is that the data resources available to the Agency do not capture use of use of Ferrlecit® or other injectable iron products in the outpatient clinic setting. Outpatients clinics appears to represent approximately three-quarters of the total use of Ferrlecit®, which is a very substantial gap in our analysis.

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